

Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
Page 5

Remarks

Introduction

The claims have been amended. Claims 23 and 25-27 have been amended to more clearly set forth the subject matter of the invention. New Claim 28 has been added. Claims 7-19 have been cancelled, without prejudice. Applicants reserve the right to pursue the subject matter of claims 7-19 in a divisional application. Claims 27, 5-6, 20-26, and 28 are currently pending. Claim 27 is the sole independent claim.

Section 112 rejections

Claims 23-25

Claims 23-25 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner alleges that "one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 27 due to the unpredictability of the role of the inhibition of cellular levels of amyloid β , and since the treatment of Alzheimer's disease is mediated by the breakdown of acetylcholine or the inhibition of excess amounts of glutamate." Applicants respectfully submit that the amendments to claims 23 and 25 obviate these grounds of rejection.

As the Examiner has pointed out, there are only two types of drugs which the United States Food and Drug Administration (FDA) has approved for treatment of Alzheimer's Disease. Both are directed toward neurotransmitter deficiencies. The first type (including Aricept, Exelon, Reminyl, and Cognex) delays the breakdown of acetylcholine, and the second type (Memantine) is directed toward inhibition of glutamate which can damage nerve cells.

However, FDA approval is not alone determinative of whether a particular therapy is an effective treatment of a disease. The delay in FDA approval of Memantine is a good example. Memantine was available for treatment of Alzheimer's in Germany for two decades prior to FDA approval. This does not reflect on the ability of the drug's performance as an effective treatment of Alzheimer's, but on the other hand, is merely reflective of a delay in satisfying the FDA's criteria to demonstrate the drug's safety and efficacy.

Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
Page 6

The current state of the art clearly demonstrates that accumulation of amyloid β protein in the brain is a cause of Alzheimer's Disease, as well as other diseases. Several medical journal articles and United States Patents have been attached to this response, which support this. As is shown below, amyloid β protein deposits contribute to many similar conditions attributed to the production of amyloid β , including amyloid angiopathy, cerebral amyloid angiopathy, systemic amyloidosis, hereditary cerebral hemorrhage with amyloidosis of the Dutch type, inclusion body myositis, and Down's syndrome.

U.S. Patent No. 6,670,182, column 1, lines 48-55:

"A characteristic feature of Alzheimer's disease is the formation or deposit of β -amyloid plaques in affected individuals. Mature β -amyloid plaques are often associated with degenerating neuronal processes. β -amyloid deposits are not solely associated with persons suffering from Alzheimer's disease but are also associated with persons suffering from other amyloidoses, for example, brain trauma or Downs syndrome."

U.S. Patent No. 6,607,758, column 1, lines 27-29:

"Accumulating evidence implicates amyloid as a major causative factor of Alzheimer's disease pathogenesis."

Column 1, lines 51-55:

"The amyloid diseases include, but are not limited to, the amyloid associated with Alzheimer's disease, Down's syndrome and hereditary cerebral hemorrhage with amyloidosis of the Dutch type."

U.S. Patent No. 6,673,600, column 2, lines 1-2:

"There is a large amount of evidence that A β peptide is a crucial factor in the development of Alzheimer's disease."

Berger, Abi. "Amyloid Clearly Implicated in Alzheimer's Disease" *British Medical Journal*, July 11, 1998:

Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
Page 7

"Dr. Geula and colleagues have now shown that not only is B amyloid present in Alzheimer's disease, but it is almost definitely causative."

Conova, Susan. "Is Alzheimer's an Astrocyte Disease?" *In Vivo*, Columbia University Health Sciences, Vol. 2, No. 6, March 26, 2003:

"Alzheimer's, most researchers believe, is caused when a small peptide, beta-amyloid, accumulates in the brain."

After considering the abundance of research demonstrating that amyloid β is a cause of Alzheimer's, it logically follows that to reduce or prevent amyloid β accumulation in the brain will prevent or improve the condition of one suffering from or at risk for developing Alzheimer's or another amyloid β related disease. In fact, several U.S. patents claim methods of treating Alzheimer's by inhibiting amyloid β . These include U.S. Patent No. 6,469,055, claim 2; U.S. Patent No. 6,311,408, claim 54; and U.S. Patent No. 6,607,758; claim 8.

All of the above listed U.S. patents conducted *in vitro* assays to demonstrate activity inhibiting amyloid β . Conducting *in vitro* assays are well-known and accepted in the art as a method of testing the activity of a particular compound. If a particular compound demonstrates a desired activity in an *in vitro* assay, it is indicative that the compound will possess the same activity *in vivo*. By demonstrating the activity by *in vitro* assay, the Applicants in each of the above-referenced patents were able to satisfy the enablement requirement of Section 112, first paragraph.

Similarly, in the present invention, *in vitro* assays were conducted to show the activity of the compounds of the present invention. As shown in example 636, the compounds of the present invention were tested for and demonstrated the ability to inhibit amyloid beta production.

The state of the art reflects that amyloid β is a causative factor in Alzheimer's disease and that preventing or removing amyloid β plaques would provide a treatment for those afflicted with

Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
Page 8

the disease, or similar amyloid β related diseases. Therefore, Applicants submit that Claims 23-25 meet the enablement requirement of Section 112, first paragraph. Reconsideration and withdrawal of the rejections of claims 23-25 are therefore appropriate and respectfully requested.

Claims 21-22

Claims 21-22 have also been rejected under 35 U.S.C. §112, first paragraph, as not meeting the enablement requirement. Specifically, the Examiner states, "the specification, while being enabling for the inhibition of proteolytic cleavage of amyloid beta precursor protein does not reasonable provide enablement for the modulating of the level of amyloid beta precursor protein, either by increasing or decreasing." Applicants respectfully submit that the clarifying amendment of claim 21 obviates this rejection.

It is well-known in the art that by administering a compound that exhibits inhibitory activity of another compound, that the other compound will likely decrease upon said administration. Similarly, after administering said first compound, if the amount of the administration of the compound is decreased or ceased, an increase in the other compound will likely result. This is method of modulation.

The Examiner had acknowledged that the compounds of the present invention demonstrate inhibitory activity to proteolytic cleavage of amyloid beta precursor protein, which is the mechanism for the production of amyloid beta. This is pointed out in the specification at page 1, line 21. The method of modulation of amyloid beta by administering a compound of the present invention would then be within the means of one of skill in the art. Therefore, reconsideration and withdrawal of the rejections of claims 21-22 are therefore appropriate and respectfully requested.

Claim 26

Claim 26 has been rejected under 35 U.S.C. §112, first and second paragraphs as failing to comply with the written description requirement and as being indefinite, respectively.

Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
Page 9

Specifically, the Examiner states that the alleged "abbreviation," "A β " is not defined in the specification. Applicants respectfully submit that the amendment of claim 26 obviates this ground of rejection by clarifying the meaning of "A β ," which is synonymous with amyloid β .

"A β " is not an unsupported abbreviation as the Examiner suggests. The meaning of "A β " is readily ascertained from the context in which it is used in the application. In the paragraph that the Examiner points out at page 311, the terms "A β " and amyloid β are used interchangeably and both directed toward explanation of the assay to determine inhibition of production of amyloid beta.

Furthermore, "A β " is a well-known term used to describe the same protein as the term amyloid β . This is demonstrated by a number of references and U.S. patents. These references are found in U.S. Patent No. 6,673,600, column 1, line 26; U.S. Patent No. 6,331,408, column 1, line 53, and in the Merck Frosst abstract of *Cell* 97 (1999): 395-406.

Considering that the term "A β " is well-known in the art and supported in the specification, Applicants submit that one of skill in the art would recognize that "A β " refers to the same protein as the term amyloid β . However, for the sake of consistency, claim 26 has been amended by replacing the term "A β " with "amyloid β ." This amendment is clearly not a narrowing amendment. Therefore, reconsideration and withdrawal of the rejections of claim 26 are appropriate and respectfully requested.

Section 102 rejections

Claims 27, 5, and 6 have been rejected under 35 U.S.C. §102(b) as being anticipated by Linfield et al. Applicants respectfully submit that the amendment to claim 27 obviates this ground of rejection. Reconsideration and withdrawal of the rejections are, therefore, appropriate and respectfully requested.

Applicant: Smith et al.
Application No: 09/890,927
Docket No: 1188-67 PCT/US
Page 10

RECEIVED
CENTRAL FAX CENTER

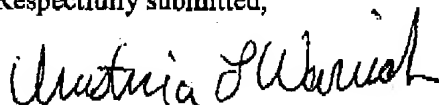
JUL 12 2004

OFFICIAL

No fee is believed due with this submission. However, please charge any additional fees to our Deposit Account No. 08-2461.

In view of the amendments and remarks set forth above, reconsideration and withdrawal of the rejections are appropriate and respectfully requested. Applicants submit the present claims are patentably distinct over the art and allowable in form. Early allowance is therefore solicited. The Examiner is encouraged to contact the undersigned attorney should there be any questions regarding this amendment.

Respectfully submitted,



Christina L. Warrick
Registration No. 45,690
Attorney for Applicant(s)

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700